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Synthesis and Structure–Activity Relationships of Miticidal 4,5-Dihydropyrazole-5-thiones

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Abstract: A series of novel 4,5-dihydropyrazole-5-thiones (DHPs) was synthesised by treating the corresponding dihydropyrazolones with Lawesson's reagent and evaluated for miticidal activity against two-spotted spider mites (*Tetranychus urticae* Koch). Of these, 3-(4-chlorophenyl)-4,4-dimethyl-1-phenyl-4,5-dihydropyrazole-5-thione, 3-(4-chlorophenyl)-4-ethyl-4-methyl-1-phenyl-4,5-dihydropyrazole-5-thione, 3-(4-chlorophenyl)-1-phenyl-4,5-dihydropyrazole-5-thione-4-spirocyclopentane and 4,4-dimethyl-1-phenyl-3-(4-trifluoromethylphenyl)-4,5-dihydropyrazole-5-thione were highly active ($pEC_{50} > 4{\cdot}0$) and were more effective than the miticide dicofol ($pEC_{50} = 3{\cdot}879$), which has traditionally been used for the control of phytophagous mites. Structure–activity relationship (SAR) studies were performed on each position of the pyrazole ring of DHPs. The results indicated that the unsubstituted phenyl, 4-substituted phenyl and thioxo groups on the 1-, 3- and 5-positions of DHPs respectively were required for activity. Quantitative SAR studies using physicochemical parameters of substituents and the capacity factor k' as a hydrophobicity index suggested that: (a) the activities of all types of DHPs examined were mainly dominated by hydrophobicity, (b) the bulkiness of 4-substituents of the 3-phenyl ring favoured the activity and (c) the log k' optimum for all DHPs was 1·675, equivalent to a log P_{ow} value of *c.* 5·0.

Key words: 4,5-Dihydropyrazole-5-thione, miticide, structure–activity relationship, *Tetranychus urticae* Koch

1 INTRODUCTION

Many kinds of pyrazole have been studied for use in agricultural fields[1–3] and developed as agrochemicals.[4–7] Although an extensive literature[8–14] has been reported on the 4,4-disubstituted 4,5-dihydropyrazol-5-ones as agrochemicals, no report about the corresponding pyrazole-5-thiones has yet been published to our knowledge. The novelty of the pyrazolethiones led us to the synthesis of several derivatives. Our primary screenings revealed that 4,5-dihydropyrazole-5-thiones (DHPs) effectively controlled mites such as two-spotted spider mites (*Tetranychus urticae* Koch), kanzawa spider mites (*Tetranychus kanzawai* Kishida), citrus red mites (*Panonychus citri* McGregor) and European red mites (*Panonychus ulmi* Koch) while 4,5-dihydropyrazol-5-ones were almost inactive. Therefore, a series of DHPs (Fig. 1) was synthesised and evaluated for miticidal activity against two-spotted spider mites (*T. urticae*) in detail. The structure–activity relationships (SARs) in DHPs were studied using physicochemical parameters of substituents and the capacity factor

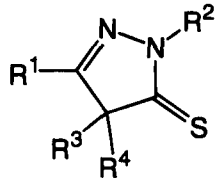

Fig. 1. General structure of 4,4-disubstituted 4,5-dihydropyrazole-5-thiones.

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k' [15–17] as a hydrophobicity index. In this paper, synthesis, miticidal activity and SAR studies of DHPs are described.

2 MATERIALS AND METHODS

2.1 Chemicals

2.1.1 General

Compounds containing an asymmetric carbon atom were obtained as racemic mixtures. Proton nuclear magnetic resonance ([^{1}H]NMR) spectra were recorded on an HR R-24B NMR spectrometer (Hitachi Corp., Tokyo, Japan) in deuterochloroform; chemical shifts (δ) were in ppm relative to tetramethylsilane as the internal standard, and coupling constants (J) were given in Hz. Melting points were measured with a model MP-2 melting point apparatus (Yamato Scientific Co. Ltd, Tokyo, Japan) and were uncorrected. Refractive indices were measured with an Abbe-3L refractometer (Bausch & Lomb Inc., NY, USA). The melting points (m.p.) and refractive indices (n_D^{20}) of DHPs are shown in Tables 1–5.

2.1.2 Synthesis

The target compounds were prepared according to the synthetic scheme shown in Fig. 2. Dihydropyrazolones were obtained by cyclisation *via* hydrazones which were given by condensing β-ketoesters and hydrazines. DHPs were prepared by treating the corresponding dihydropyrazolones with Lawesson's reagent[18] (purchased from Wako Pure Chemical Industries Ltd, Osaka, Japan). Processes of DHP preparation were classified into three routes: route I, procedures A, C and E; II, B and E and III, B, D and E. The synthetic routes utilised are listed in Tables 1–5. Details of a typical example of each procedure shown in Fig. 2 are as follows:

Procedure A: Synthesis of 3-(4-chlorophenyl)-4,4-dimethyl-4,5-dihydropyrazol-5-one (Fig. 2; $R^1 = 4\text{-}ClC_6H_4$, $R^3 = R^4 = CH_3$)

A solution of ethyl 2-(4-chlorobenzoyl)-2-methylpropionate (22·5 g, 49·0 mmol) and hydrazine monohydrate (12·5 g, 250 mmol) in ethanol (100 ml) was stirred and refluxed. After 24-h reflux, the reaction mixture was concentrated under vacuum. The residual solid was washed successively with water, 50% ethanol and diethyl ether, and then dried under vacuum in the presence of phosphorus pentoxide to afford an off-white solid: 19·1 g (86%); m.p. 145–146°C; [^{1}H]NMR δ: 1·51 (s, 6H, $C(CH_3)_2$), 7·39 (d, 2H, J = 9·0 Hz, Ph-H), 7·75 (d, 2H, J = 9·0 Hz, Ph-H), 9·00 (br s, 1H, NNHCO).

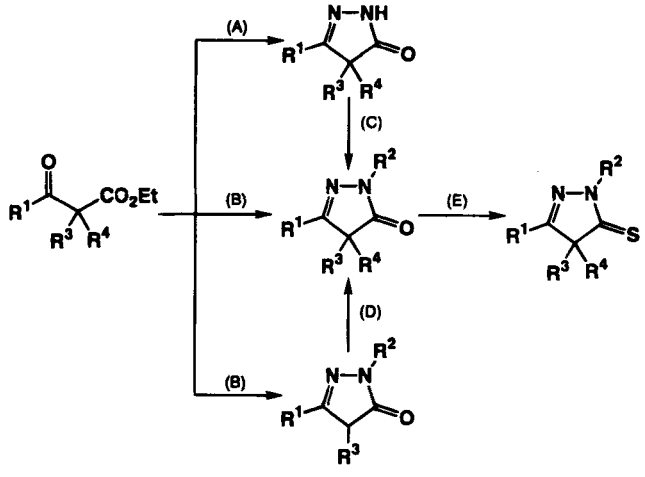
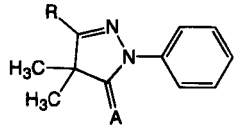


Fig. 2. Routes for the synthesis of 4,4-disubstituted 4,5-dihydropyrazole-5-thiones.

TABLE 1

Effect of Substituents at the 3- and 5-Position of Dihydropyrazoles on Miticidal Activity against *Tetranychus urticae*



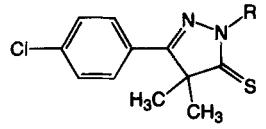
Compound	*R*	*A*	*Synthetic route*[a]	*M.p.*(°C)	pEC_{50}[b] (±*S.D.*)
1	CH_3	S	II	45–46	<2·339
2	$CH_2C_6H_5$	S	II	96–97	<2·469
3	C_6H_5	S	II	121–123	3·630 (±0·195)
4	2-ClC_6H_4	S	II	87–89	3·334 (±0·015)
5	3-ClC_6H_4	S	II	89–90	3·974 (±0·109)
6	4-ClC_6H_4	S	II	146–147	4·089 (±0·067)
7	4-ClC_6H_4	O	B[c]	97–99	<2·475
dicofol		—	—	—	3·879 (±0·088)

[a] See Section 2.1.2.

[b] Log (M required for a 50% mortality)$^{-1}$.

[c] Synthesised *via* procedure B.

TABLE 2
Effect of Substituents at the 1-Position of DHPs on Miticidal Activity against *Tetranychus urticae*



Compound	*R*	*Synthetic route*[a]	*M.p.* (°C) *or* n_D^{20}	pEC_{50} (±*S.D.*)	*Log* k'[b]
6	C_6H_5	II	146–147	4·088 (±0·067)	1·545
8	H	II	172–173	2·710 (±0·009)	0·579
9	CH_3	I	94–95	3·377 (±0·031)	0·911
10	CH_2CH_3	I	45–47	3·599 (±0·071)	1·207
11	$CH_2CH_2CH_3$	I	74–75	3·574 (±0·029)	1·408
12	$CH(CH_3)_2$	I	68–69	3·529 (±0·010)	1·391
13	$C(CH_3)_3$	II	51–52	3·747 (±0·041)	1·721
14	$CH_2CH_2CH(CH_3)_2$	I	1·615	3·721 (±0·044)	1·811
15	$CH_2(CH_2)_4CH_3$	I	1·607	3·677 (±0·013)	2·060
16	$CH_2CH=CH_2$	I	1·651	3·619 (±0·071)	1·226
17	$CH_2CO_2CH_3$	I	77–75	3·580 (±0·032)	0·856
18	$CH_2CO_2C(CH_3)_3$	I	62–63	3·735 (±0·013)	1·380
19	$CH_2COC(CH_3)_3$	I	107–108	3·678 (±0·037)	1·238

[a] See Section 2.1.2.
[b] Log (capacity factor *k'*), see Section 2.3.1.

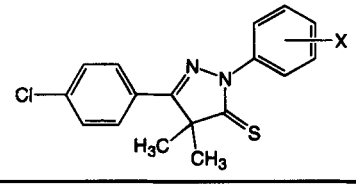
Procedure B: Synthesis of 3-(4-chlorophenyl)-4,4-dimethyl-1-phenyl-4,5-dihydropyrazol-5-one (R^1 = 4-ClC_6H_4, $R^2 = C_6H_5$, $R^3 = R^4 = CH_3$)

A solution of ethyl 2-(4-chlorobenzoyl)-2-methyl-propionate (1·5 g, 5·9 mmol) and phenylhydrazine (0·8 g, 7·4 mmol) in toluene (20 ml) was stirred and refluxed in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate to remove water with a Dean-Stark apparatus. After 16 h reflux, the reaction mixture was concentrated under vacuum. The residue dissolved in acetic acid (10 ml) was refluxed for 4 h. After evaporation of the solvent, the residue was extracted with diethyl ether. The extract was washed successively with 3% hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residual solid was recrystallised from ethanol to afford an off-white solid: 1·3 g (71%); m.p. 97–99°C; [^{1}H]NMR δ: 1·57 (s, 6H, $C(CH_3)_2$), 7·10–8·10 (m, 9H, Ph-H).

Procedure C: Synthesis of 3-(4-chlorophenyl)-4,4-dimethyl-1-*n*-propyl-4,5-dihydropyrazol-5-one (R^1 = 4-ClC_6H_4, $R^2 = CH_2CH_2CH_3$, $R^3 = R^4 = CH_3$)

To a suspension of sodium hydride (60% in oil, 0·22 g, 5·5 mmol) in dry *N,N*-dimethylformamide (DMF, 10 ml) cooled at 0°C was added a solution of 3-(4-chlorophenyl)-4,4-dimethyl-4,5-dihydropyrazol-5-one (1·0 g, 4·5 mmol) in dry DMF (5 ml), and the

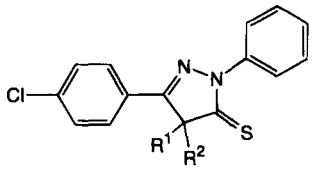
TABLE 3
Positional Effect of the Chloro Substituent on the 1-Phenyl Ring of DHPs on Miticidal Activity against *Tetranychus urticae*



Compound	*X*	*Synthetic route*[a]	*M.p.* (°C)	pEC_{50} (±*S.D.*)	*Log* k'
6	H	II	146–147	4·088 (±0·067)	1·545
20	2-Cl	II	140–141	3·910 (±0·010)	1·354
21	3-Cl	II	81–82	3·862 (±0·009)	1·931
22	4-Cl	II	90–91	3·822 (±0·130)	1·920

[a] See Section 2.1.2.

TABLE 4
Effect of Substituents at the 4-Position of DHPs on Miticidal Activity against *Tetranychus urticae*

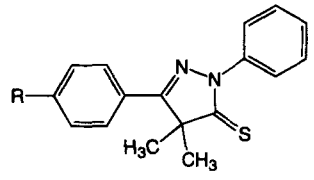


Compound	R^1	R^2	*Synthetic route*[a]	*M.p.* (°C)	pEC_{50} (±*S.D.*)	*Log* k′
6	CH_3	CH_3	II	146–147	4·088 (±0·067)	1·545
23	CH_3	CH_2CH_3	II	55–56	4·130 (±0·157)	1·649
24	CH_3	$CH_2CH_2CH_3$	II	83–85	3·983 (±0·061)	1·847
25	CH_3	$CH_2(CH_2)_2CH_3$	II	70–72	3·930 (±0·021)	2·015
26	CH_2CH_3	CH_2CH_3	II	66–68	3·970 (±0·088)	1·756
27		$-(CH_2)_4-$	II	115–117	4·083 (±0·069)	1·843
28	CH_3	CO_2CH_3	II	109–110	4·005 (±0·073)	1·352
29	CH_3	$CH_2CO_2CH_3$	III	68–70	3·583 (±0·007)	1·117

[a] See Section 2.1.2.

mixture was stirred for 30 min. To the mixture was added dropwise *n*-propyl bromide (0·83 g, 6·7 mmol) at 0°C, and the mixture was stirred for 3 h at room temperature. The reaction mixture was poured into ice water, and then the mixture was extracted three times with diethyl ether. The extracts were combined, washed with brine and dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane + ethyl acetate, 4 + 1 by volume) to afford a colourless oil: 1·1 g (92%); [^{1}H]NMR δ: 0·96 (t, 3H,

TABLE 5
Effect of 4-Substituents of the 3-Phenyl Ring of DHPs on Miticidal Activity against *Tetranychus urticae*



Compound	*R*	*Synthetic route*[a]	*M.p.* (°C) *or* n_D^{20}	pEC_{50} (±*S.D.*)	*Log* k′	B1[b]
3	H	II	121–123	3·630 (±0·195)	1·271	1·00
6	Cl	II	146–147	4·088 (±0·067)	1·545	1·80
30	F	II	79–80	3·700 (±0·004)	1·273	1·35
31	Br	II	112–113	4·006 (±0·018)	1·616	1·95
32	CF_3	II	107–108	4·095 (±0·016)	1·577	1·98
33	CH_3	II	112–113	3·794 (±0·041)	1·495	1·52
34	CH_2CH_3	II	95–96	3·786 (±0·022)	1·694	1·52
35	$CH(CH_3)_2$	II	102–103	3·823 (±0·062)	1·862	2·04
36	$CH_2(CH_2)_2CH_3$	II	1·648	3·400 (±0·023)	2·148	1·52
37	$C(CH_3)_3$	II	113–114	3·979 (±0·133)	2·013	2·59
38	OCH_3	II	67–69	3·564 (±0·031)	1·263	1·35
39	$OCH_2CH_2CH_3$	II	70–71	3·928 (±0·154)	1·727	1·35
40	$OCH_2(CH_2)_2CH_3$	II	72–73	3·802 (±0·112)	1·961	1·35
41	OC_6H_5	II	88–89	3·755 (±0·108)	1·883	1·35
42	CN	II	147–148	3·054 (±0·008)	0·966	1·60
43	CO_2CH_3	II	98–99	3·703 (±0·071)	1·316	1·90
44	$CO_2CH_2CH_3$	II	93–94	3·861 (±0·195)	1·513	1·90

[a] See Section 2.1.2.
[b] Verloop's STERIMOL parameter cited from Ref. 24.

J = 7·2 Hz, CH_2CH_3), 1·52 (s, 6H, $C(CH_3)_2$), 1·40–2·10 (m, 2H, $CH_2CH_2CH_3$), 3·72 (t, 2H, J = 9·0 Hz, NCH_2CH_2), 7·32 (s, 2H, J = 9·0 Hz, Ph-H), 7·69 (d, 2H, J = 9·0 Hz, Ph-H).

Procedure D: Synthesis of 3-(4-chlorophenyl)-4-methoxycarbonylmethyl-4-methyl-1-phenyl-4,5-dihydropyrazol-5-one (R^1 = 4-ClC_6H_4, R^2 = C_6H_5, R^3 = CH_3, R^4 = $CH_2CO_2CH_3$)

To a suspension of sodium hydride (60% in oil, 0·34 g, 8·5 mmol) in dry tetrahydrofuran (5 ml) cooled at −40°C was added a solution of 3-(4-chlorophenyl)-4-methyl-1-phenyl-4,5-dihydropyrazol-5-one (2·0 g, 7·0 mmol, prepared in a manner similar to procedure B) dissolved in dry tetrahydrofuran (10 ml), and the mixture was stirred for 1 h. To the mixture was added dropwise methyl bromoacetate (1·3 g, 8·5 mmol) at 0°C, and then this mixture was stirred for 18 h at room temperature. The reaction mixture was poured into ice water, and then the mixture was extracted three times with diethyl ether. The extracts were combined, washed with brine and dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane + ethyl acetate, 3 + 1 by volume) to afford a white solid: 1·2 g (50%); m.p. 123–124°C; [^{1}H]NMR δ: 1·54 (s, 3H, CCH_3), 3·60 (d, 2H, J = 3·0 Hz, CCH_2CO_2), 3·43 (s, 3H, CO_2CH_3), 7·00–8·05 (m, 9H, Ph-H).

Procedure E: Synthesis of 3-(4-chlorophenyl)-4,4-dimethyl-1-phenyl-4,5-dihydropyrazole-5-thione (R^1 = 4-ClC_6H_4, R^2 = C_6H_5, R^3 = R^4 = CH_3)

A solution of 3-(4-chlorophenyl)-4,4-dimethyl-1-phenyl-4,5-dihydropyrazol-5-one (1·0 g, 3·3 mmol) and Lawesson's reagent[18] (1·2 g, 3·0 mmol) in toluene (15 ml) was stirred and refluxed. After 2 h reflux, the mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane + ethyl acetate, 8 + 1 by volume), and the product was recrystallised from a mixture of diethyl ether and hexane (1 + 4 by volume) to afford a yellow solid: 1·0 g (95%); m.p. 102–103°C; [^{1}H]NMR δ: 1·65 (s, 6H, $C(CH_3)_2$) 7·20–7·70 (m, 5H, Ph-H), 7·80–8·20 (m, 4H, Ph-H).

2.2 Biological test

The activity of the compounds against two-spotted spider mite (*T. urticae*) was evaluated. A thick cotton cloth (4·5 × 5·5 cm) with a strip (1 × 4 cm) was placed on the lid of a KP-120 plastic cup (*c.* 7 cm ID, Kohnoike Plastic Co. Ltd, Osaka, Japan) containing distilled water (40 ml), and the strip was steeped in the water through the slit of the lid. A leaf segment (2 × 3 cm) was cut from 14-day-old kidney bean (*Phaseolus vulgaris* L. cv. Shin-Edogawa) and placed on the cloth. The test compound was dissolved in acetone and stored at 6°C in the dark until use. To prepare a spray solution containing the test compound (10–300 mg litre^{-1}), an appropriate amount of the stock solution was diluted with acetone up to 0·1 ml and aqueous 'Tween 80' (100 mg litre^{-1}; 1·9 ml) was added. Twenty adult mites were settled in the leaf segment. After one day at 23(±2)°C, the spray solution (2 ml) was applied to the mites through a transparent acrylic cylinder (30 × 12 cm ID) at 270 mm Hg with a spray tower (Mizuho-Rika Co. Ltd, Nagoya, Japan), and then the cups were placed in an assay room at 25°C and 50% RH under two Toshiba FL40S-D fluorescent lamps (75–91·5 μE m^{-2} s^{-1} PAR) with a 16/8 h light/dark cycle. Two days after treatment, the number of live, dead and moribund mites was counted. Experiments were repeated until acceptable sigmoidal response curves were obtained, applying, on average, five concentrations for a compound at a time. Controls were treated with 2 ml of aqueous 'Tween 80' (100 mg litre^{-1}) containing acetone (5% by volume). The mortality, including moribund mites, was corrected using Abbott's formula.[19] A pEC_{50} value was defined as the negative logarithm of the molar concentration required for 50% mortality and obtained from the data points of the above-mentioned curves by Litchfield–Wilcoxon's method.[20] The pEC_{50} values given in the tables are means (±standard deviations) from two pEC_{50} values. The commercial miticide dicofol (2,2,2-trichloro-1,1-bis(4-chlorophenyl)ethanol)[21,22] was used in all tests as a reference since it has long been widely used for the control of phytophagous mites.

2.3 Hydrophobicity

2.3.1 High-performance liquid chromatographic (HPLC) method.[15–17]

The HPLC instruments used were composed of an L-6000 pump, a D-2500 recorder, an L-4000 UV detector, an L-5020 column oven (all from Hitachi Corp., Tokyo, Japan) and a model 7125 injector with a 20-μl loop (Rheodyne Inc., Cotati, CA, USA). Detection was done at 350 nm and a sensitivity of 4–128 mV. A Zorbax BP-ODS column (4·6 × 250 mm, Sumitomo Chemical Analysis Service Ltd, Osaka, Japan) was used at 40°C. A mixture of methanol and water (7 + 3 by volume) was used as a mobile phase, and the flow rate was 1·0 ml min^{-1}. A 10-μl sample solution (1 g litre^{-1}) was analysed, and the retention time was used to calculate the capacity factor k' as follows:

$$k' = (t_R - t_0)/t_0$$

where t_R and t_0 were the retention times of the test compound and potassium iodide respectively. The logarithm of k' was used as a hydrophobicity index, and values are listed in Tables 2–5.

2.3.2 Octanol–water partition coefficient
The octanol–water partition coefficient (P_{ow}) was determined by the method of Imai *et al.*[23] The HPLC instruments and the conditions were the same as in Section 2.3.1 except for the use of an Inertsil ODS-80A column (4·6 × 250 mm, GL Sciences Inc., Tokyo, Japan) and a mixture of acetonitrile and water (9 + 1 by volume) as a mobile phase.

3 RESULTS AND DISCUSSION

3.1 Synthesis

Reaction of α,α-disubstituted β-ketoesters with phenylhydrazines afforded hydrazones and the corresponding dihydropyrazolones which are produced by cyclisation of the hydrazones. However, the cyclisation in toluene was incomplete even after 24 h reflux. The use of acetic acid instead of toluene as solvent led to completion of the cyclisation in a few hours. This suggests that acidic polar solvents such as acetic acid may be more suitable than nonpolar ones for the cyclisation of hydrazones to dihydropyrazolones.

Replacement of oxygen by sulfur at the 5-position of DHPs was performed by treating the dihydropyrazolone with Lawesson's reagent, and target compounds were obtained generally with high yields. Phosphorus pentasulfide could be used for the replacement reaction, but the replacement rate was slower than that with Lawesson's reagent (data not shown), probably because of the low solubility in the solvents used, such as benzene, toluene and carbon disulfide.

3.2 Structure–activity relationships (SARs)

When phenyl and dimethyl groups were fixed to the 1- and 4-positions of DHPs respectively, the effect of substituents at the 3-position and the thioxo group at the 5-position of DHPs on miticidal activity against *T. urticae* was investigated. The biological data are shown in Table 1. The phenyl derivative **3** was active, and the methyl (**1**) and benzyl (**2**) derivatives were inactive. The 4-chlorophenyl derivative **6**, which was superior to the reference dicofol, and the 3-chloro derivative **5** had high activity, while the 2-chlorophenyl derivative **4** showed only weak activity. The latter may be ascribed to lack of coplanarity between the pyrazole and 3-(2-chlorophenyl) rings. The oxo compound **7**, which was the precursor of compound **6**, was inactive. All the other oxo compounds were also inactive (data not shown). These results suggest that the phenyl and thio groups at the 3- and 5-positions of DHPs, respectively, were required for miticidal activity and that the 3- or 4-substituent of the 3-phenyl ring was favourable for the activity. The 3-(4-chlorophenyl) derivatives were selected for further studies because of the high activity of compound **6**.

The influence of substituents at the 1-position of DHPs on the miticidal activity was investigated when the dimethyl groups were fixed to the 4-position. Multiple regression analysis was performed on the activities of compounds **6** and **8**–**19** (Table 2), using log k' values and the physicochemical parameters of substituents such as Verloop's STERIMOL *B1*, *B4* and *L*,[24] and electronic *R* and *F*,[25] and eqn (1) was obtained at the 95% confidence level.

$$p\mathrm{EC}_{50} = -0{\cdot}829\ (0{\cdot}249) \times \log k'^2 + 2{\cdot}713\ (0{\cdot}667) \times \log k' + 1{\cdot}569\ (0{\cdot}429)$$
$$n = 13,\ r = 0{\cdot}867,\ s = 0{\cdot}169 \text{ and } F_{2,10} = 15{\cdot}141 \quad (1)$$

In eqn (1) and following equations, n is the number of the compounds used, r is the correlation coefficient, s is the standard deviation and $F_{m,n-m-1}$ is the F ratio, where m is the number of independent variables. The values in parentheses are the 95% confidence intervals. Equation (1) correlates the activity and the hydrophobicity as shown in Fig. 3, yielding a log k' optimum of 1·636. Except for log k', none of the other parameters examined was related to the activity. Compound **6** showed the highest activity, having a log k' value of 1·545, near the optimum 1·666.

The positional effect of the chloro substitution of the 1-phenyl ring on the activity was also examined. The activities of the 2-chloro (**20**), 3-chloro (**21**) and 4-chloro (**22**) derivatives were weaker than the activity of the unsubstituted one (**6**) (Table 3). The substitution on the 1-phenyl ring of DHPs was suggested to be unfavourable for activity.

To evaluate the effect of alkyl substituents at the 4-position on miticidal activity, regression analysis was

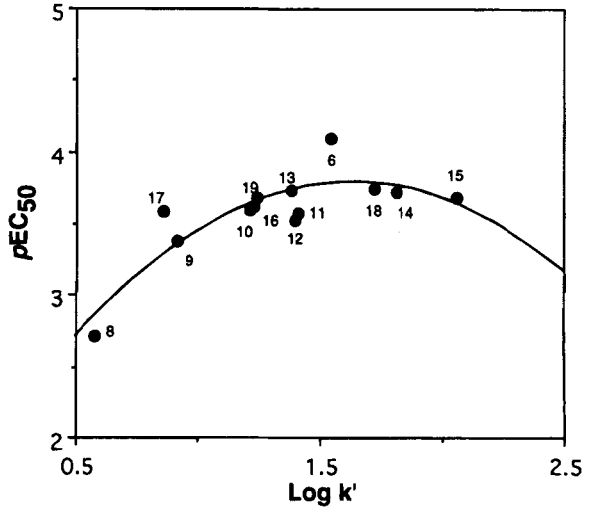


Fig. 3. Log k' versus $p\mathrm{EC}_{50}$ of 1-substituted 3-(4-chlorophenyl)-4,4-dimethyl-4,5-dihydropyrazole-5-thiones against *Tetranychus urticae*.

done on compounds **6** and **23–29** (Table 4), and eqn (2) was obtained.

$$pEC_{50} = -1{\cdot}633\ (0{\cdot}337) \times \log k'^2 + 5{\cdot}416\ (1{\cdot}056) \times \log k' - 0{\cdot}394\ (0{\cdot}807)$$
$$n = 8,\ r = 0{\cdot}937,\ s = 0{\cdot}071 \text{ and } F_{2,5} = 17{\cdot}847 \quad (2)$$

Equation (2) indicates that the activity is closely correlated with log k', as shown in Fig. 4, yielding a log k' optimum of 1·658. The dimethyl (**6**), ethyl-methyl (**23**) and spiro-cyclopentane (**27**) derivatives were more active than the others, having hydrophobicity around the log k' optimum. The dimethyl derivative **6** was selected as a lead because of the absence of chiral carbon at the 4-position as well as the high activity.

Finally, the effect of 4-substituents of the 3-phenyl ring on miticidal activity was examined. The analysis of compounds **3**, **6** and **30–44** (Table 5) yielded eqn (3).

$$pEC_{50} = -1{\cdot}891\ (0{\cdot}267) \times \log k'^2 + 6{\cdot}300\ (0{\cdot}851) \times \log k' - 1{\cdot}296\ (0{\cdot}662)$$
$$n = 17,\ r = 0{\cdot}902,\ s = 0{\cdot}119 \text{ and } F_{2,14} = 30{\cdot}654 \quad (3)$$

Equation (3) shows a parabolic correlation between the activity and log k' (Fig. 5), of which the optimum is 1·666. Introduction of the electronic parameter F or R into eqn (3) failed to improve the equation, while the addition of $B1$ term, the minimum radius of substituent, enhanced the quality of the equation, giving eqn (4).

$$pEC_{50} = -1{\cdot}852\ (0{\cdot}216) \times \log k'^2 + 6{\cdot}115\ (0{\cdot}691) \times \log k' + 0{\cdot}192\ (0{\cdot}066) \times B1 - 1{\cdot}419\ (0{\cdot}536)$$
$$n = 17,\ r = 0{\cdot}942,\ s = 0{\cdot}096 \text{ and } F_{3,13} = 34{\cdot}130 \quad (4)$$

There was no colinearity of the $B1$ with log k'^2 and log k', and the log k'^2, log k' and $B1$ terms were found

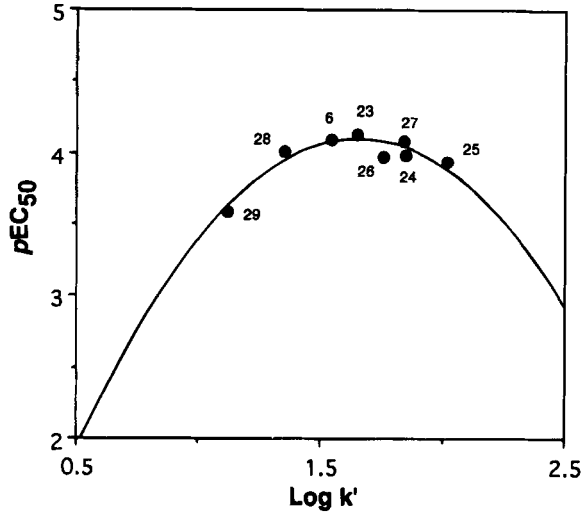


Fig. 4. Log k' versus pEC_{50} of 4,4-disubstituted 3-(4-chlorophenyl)-1-phenyl-4,5-dihydropyrazole-5-thiones against *Tetranychus urticae*.

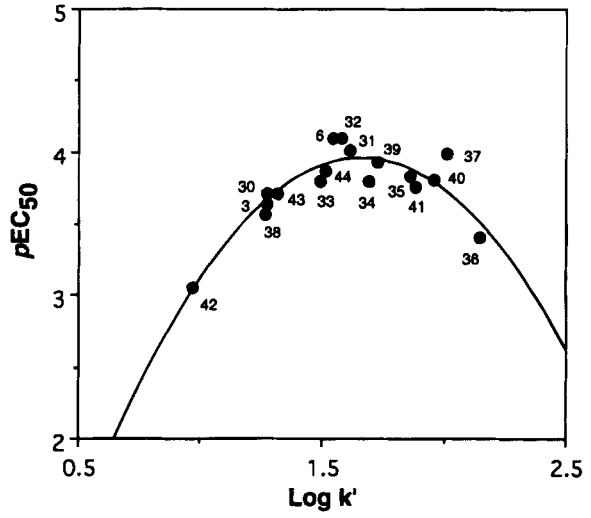


Fig. 5. Log k' versus pEC_{50} of 3-(4-substituted phenyl)-4,4-dimethyl-1-phenyl-4,5-dihydropyrazole-5-thiones against *Tetranychus urticae*.

to be significant on a t-test. Equation (4) indicates that the bulkiness of 4-substituents of the 3-phenyl ring favours the activity correlated parabolically with log k' (Fig. 6). The log k' optimum is 1·651. The chloro (**6**) and trifluoromethyl (**32**) derivatives were highly active in this series, having both log k' and $B1$ values suitable for the activity.

Equations (1)–(4) indicated that the activity was mainly dominated by hydrophobicity. The data shown in Tables 2–5 provided eqn (5).

$$pEC_{50} = -0{\cdot}956\ (0{\cdot}162) \times \log k'^2 + 3{\cdot}237\ (0{\cdot}475) \times \log k' + 1{\cdot}150\ (0{\cdot}337)$$
$$n = 39,\ r = 0{\cdot}826,\ s = 0{\cdot}162 \text{ and } F_{2,36} = 38{\cdot}591 \quad (5)$$

Equation (5) exhibits a parabolic relation of the activity with log k' (Fig. 7), of which the optimum is 1·693.

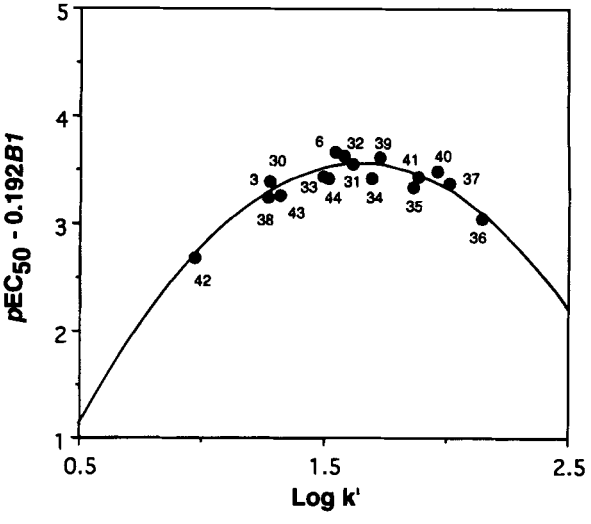


Fig. 6. Relationship of pEC_{50} of 3-(4-substituted phenyl)-4,4-dimethyl-1-phenyl-4,5-dihydropyrazole-5-thiones against *Tetranychus urticae* with log k' and the STERIMOL parameter $B1$.

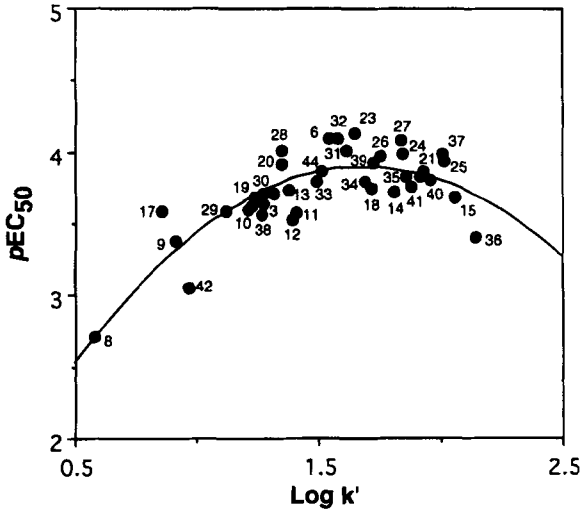


Fig. 7. Log k' versus pEC_{50} of all types of 4,5-dihydropyrazole-5-thiones against *Tetranychus urticae*.

Furthermore, the quality of the equation was improved by introducing the *B1* term into eqn (5), and eqn (6) was obtained.

$$pEC_{50} = -0{\cdot}993\ (0{\cdot}153) \times \log k'^2 + 3{\cdot}328\ (0{\cdot}448) \times \log k' + 0{\cdot}231\ (0{\cdot}097) \times B1 + 0{\cdot}701\ (0{\cdot}369)$$

$$n = 39,\ r = 0{\cdot}852,\ s = 0{\cdot}152 \text{ and } F_{3,35} = 30{\cdot}984 \quad (6)$$

The log k'^2, log k' and *B1* terms were significant at the 95% level, and *B1* was not related with either log k'^2 or log k'. The relation of the activity with these three terms is illustrated in Fig. 8, and the log k' optimum obtained from eqn (6) is 1·675. A stepwise regression analysis for the development of eqn (5) into eqn (6) indicates not only that the hydrophobicity indices account for 68% of the variance of the biological activity but also that the *B1* term further explains the variance by 5%.

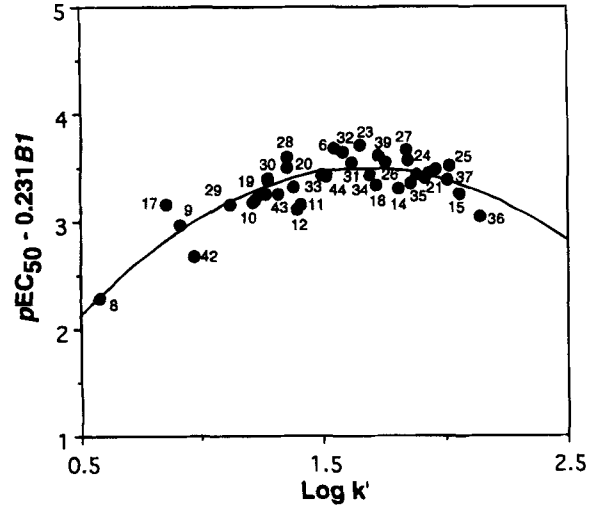


Fig. 8. Relationships of pEC_{50} of all types of 4,5-dihydropyrazole-5-thiones against *Tetranychus urticae* with log k' and the STERIMOL parameter *B1*.

Consequently, hydrophobicity was suggested to be the most important factor for miticidal activity of all types of DHPs examined, and the bulkiness of 4-substituents of the 3-phenyl ring also favoured the activity. The log k' optimum of all types of DHPs was 1·675, equivalent to *c.* 5·0 of log P_{ow} estimated by the calibration curve obtained from log k' and log P_{ow} values below 4·7 (estimation of log P_{ow} above 4·7 by the flask-shaking method used here was found to be rather difficult).

Many of the DHPs studied in the present paper showed excellent activity against two-spotted spider mites and are considered to be highly promising as miticides.

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